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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,918	LELIVELT ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41 and 43-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 43-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 41 and 43-92 are pending. Claims 67-81 and 85 are withdrawn from consideration as being drawn to a nonelected invention. Claims 41, 43-66, 82-84 and 86-92 are examined.

2. This application contains claims 67-81 and 85 drawn to an invention nonelected without traverse in the response filed 12 July 2007. A complete reply to the final rejection must include cancellation of nonelected claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The objection to claims 46 and 56-57 because of informalities is withdrawn in light of Applicant's amendment of the claims.

5. The objection to claim 53 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of Applicant's amendment of the claim.

6. The rejection of claims 41-47, 49-52, 54, 57, 61-65, 82-84 and 86-89 under 35 U.S.C. 102(b) as being anticipated by Blowers et al (WO 99/05265) is withdrawn in light of Applicant's amendment of the claims.

7. The rejection of claims 41-47, 49-52, 54, 57-65, 82-84 and 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blowers et al (WO 99/05265) in view of Maliga et al (US Patent 6,388,168) is withdrawn in light of Applicant's amendment of the claims.

Claim Objections

8. Claims 43, 54-55 and 58-63 are objected to because of the following informalities:

In claim 43, line 11, "plastid" is misspelled.

In claim 54 and 55, there is a plurals disagreement in the recitation "the DNA segments ... have a DNA sequence".

In claims 58-63, line 3, there is an improper article before "culture".

9. Claim 65 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Parent claim 41 already indicates that the culture medium containing the selection agent is a liquid medium.

10. Claim 56 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Parent claim 55 requires that the targeting DNA segment consist of the trnI(oriA)trnA and 16S/trnV/Orf70B regions. Claim 56 recites that these sequence are selected from SEQ ID NOs:6-9 and/or 13-16. However, SEQ ID NOs:6-9 and/or 13-16 are only 22-43 nucleotides long. The trnI(oriA)trnA and 16S/trnV/Orf70B regions are much larger (see the instant Fig 2). Thus, claim 56 fails to properly limit claim 55.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of lettuce plastid transformation with a vector comprising flanking sequences consisting of oligonucleotide sequences (the instant SEQ ID NOs: 6-9 and/or 13-16).

The instant specification, however, only provides guidance for a method of lettuce plastid transformation with a vector comprising flanking sequences consisting of the trnI(oriA)trnA and 16S/trnV/Orf70B regions.

The instant SEQ ID NOs:6-9 and/or 13-16 are 22-43 nucleotides long. Maliga et al (1999, US Patent 5,877,402) teach that targeting segments should be at least 50 nucleotide long and that those of 500-1500 are preferred (column 21, lines 46-55). Thus, the targeting segments claimed in claim 56 are too small to function in the claimed method.

Thus, the method of claim 56 is not enabled.

13. Claims 41, 43, 45-52 54-66 and 91-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of Asteraceae transformation where the transformation vector comprises a selection marker, does not reasonably provide enablement for a method of Asteraceae transformation where the transformation vector does not comprise a selection marker. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of Asteraceae transformation where the transformation vector does not comprise a selection marker.

The instant specification, however, only provides guidance for a method of Asteraceae transformation where the transformation vector comprises a selection marker.

Without a section marker, the transformed plant material will not survive the medium comprising the selection agent.

Further, if the selection marker is a visual marker like green fluorescent protein, there is no selection agent that can be incorporated into the medium to use a selection agent, as this marker works fluorescing light.

Thus, the instant invention is not enabled throughout the full scope of the claims.

14. Claims 43, 45, 47-52, 54-56, 86 and 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 24 September 2007. Applicant's arguments filed 25 February 2008 have been fully considered but they are not persuasive.

Claim 50 is indefinite in its recitation of "wherein the terminator is selected from the group consisting of the *psb*A, rrn, rbcL, trnV and rpsl6" as *psb*A, rrn, rbcL, trnV and rpsl6 are entire genes, not just terminators.

Applicant urges that the claim has been amended (response pg).

This is not found persuasive because *psb*A, rrn, rbcL, trnV and rpsl6 are entire genes, not just terminators. It is suggested that --from a gene-- be inserted between "is" and "selected".

The following rejections are new:

Claim 43 lacks antecedent basis for the limitations "the expression vector" in line 2, "the transforming DNA of interest" in lines 4-5, and "the plastid genome of interest" in line 11.

Claim 45 is indefinite in its recitation of "their genome". Which genome is being referred to here - plastid? Nuclear? Mitochondrial?

Claim 47 lacks antecedent basis for the limitation 'the promoter".

Claims 48-49 lack antecedent basis for the limitation "the DNA of interest".

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 49 recites the broad recitation "stress", and the claim also recites "cold, high salt or minerals" which is the narrower statement of the range/limitation.

Claim 50 lacks antecedent basis for the limitation "the terminator".

Claims 51-52 lacks antecedent basis for the limitation "the selection marker".

Claims 54 and 55 lack antecedent basis for the limitations "the DNA segments" and the "plastid genome of interest".

Claim 55 lacks antecedent basis for the limitation "the set of DNA segment".

Claim 56 lacks antecedent basis for the limitation "the set of DNA segments".

Claim 86 lacks antecedent basis for the limitation "the gene of interest".

Claim 88 lacks antecedent basis for the limitation "Plant parts as claimed in claim 82" as claim 82 only claims a plant part.

Claim Rejections - 35 USC § 103

15. Claims 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201).

The claims are drawn to a method of Asteraceae chloroplast transformation by PEG-mediated transformation of protoplasts.

Koop et al teach a method of tobacco leaf chloroplast transformation by PEG-mediated transformation of protoplasts (pg 194, left column, paragraph 4, to pg 195, left column, paragraph 2). In this method, a vector comprising an expression cassette comprising the Prrn promoter and rbcL ribosome binding site operably linked to the aadA selection marker operably linked to a termination sequence, flanked by the tobacco ndhF and trnL sequences as targeting segments that allow double homologous recombination (See Fig 1b), is transformed into tobacco protoplasts by PEG-mediated transformation. The protoplasts were embedded in alginate, then

placed in contact with a liquid medium that did not contain a selection agent (pg 195, left column, paragraph 1). After two weeks, they were transferred to solid selection medium containing spectinomycin and/or streptomycin (pg 195, left column, paragraph 1-2) and transformed plants and progeny produced.

Koop et al do not disclose a method of PEG-mediated Asteraceae plastid transformation, including transformation of lettuce with a vector containing lettuce sequences, the presence of a DNA insertion site for a sequence of interest, and a time of contact in the culture medium without a selection agent as short as two days or in the dark.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation as taught by Koop et al to apply the method to other plant species, including Asteraceae like lettuce. One of ordinary skill in the art would have been motivated to do so because Koop et al indicate that the method would be useful for a wide range of plant species (pg 201, left column paragraph 2), and because of the economic importance of such species.

At the time the invention was made, it would also have been obvious to one of ordinary skill in the art to modify the method of plastid transformation as taught by Koop et al to replace the tobacco flanking regions with the corresponding ones from the Asteraceae plastid one wishes to transform, including that of lettuce. One of ordinary skill in the art would have been motivated to do so because plastid transformation works by homologous recombination (Koop et al, pg 193, right column), and one of skill in the art would know that the higher the homology between the targeting segment and the target, the higher the probability of transformation.

One of ordinary skill in the art would have been motivated to include a DNA insertion site for receiving a DNA of interest sot that one could clone genes encoding proteins of interest into plastids. Additionally, it would be obvious to one of skill in the art to experiment with different lengths of times of exposure to the medium lacking a selection agent t, and would have tried shorter times, including for only two days, in the optimization of experimental protocols. One of ordinary skill in the art would have placed the treated plant material in contact in the liquid culture medium without a selection agent in the dark in the optimization of experimental parameters, and it is one of only two available options.

16. Claims 49-50, 55-56 and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201) as applied to claim s 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 above, and further in view of Blowers et al (WO 99/05265).

The claims are drawn to a method of lettuce plastid transformation, using the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, and particle bombardment as the transformation method.

The teachings of Koop et al are discussed above. Koop et al do not teach the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, sequences of interest providing herbicide resistance, and use of particle bombardment as the transformation method.

Blowers et al teach transformation of tobacco plastid genomes by transforming by particle gun transformation nonphotosynthetic tobacco suspension cells with a plasmid comprising an expression cassette comprising the Prrn promoter operably linked to distronic gusA-aadA or hph-aadA or tricistronic glpB-hph-aadA operably linked to the psbA terminator and flanked on one side by petunia 70B and the other by trnV/16S/trnI/trnA (Fig 3; pg 51, lines

1-9), placing the plant material for two days on medium lacking a selection agent, then transferring to medium comprising the selection agent spectinomycin or glyphosate, and maintaining the resulting calli on either solid or liquid selection media, thus, refreshing the culture medium comprising the selection agent (pg 42, line 20, to pg 44, line 22; pg 49, line 6, to pg 53, line 24; pg 54, line 1, to pg 57, line 10). The resulting transformed calli had the expression cassette inserted into the plastid genome (pg 47, lines 1-9).

The expression cassette comprises a HindIII insertion site (pg 43, lines 5-8), and the gusA coding sequence would be the gene of interest. The nonphotosynthetic tobacco suspension cells contain proplastids (pg 7, lines 2-5). GusA is a visual selection marker when the cells are grown in the correct medium. hph and glpB are genes of interest that confer resistance to the herbicide glyphosate. rps7/rsp12 and the other by trnI/trnA allow double homologs recombination of the DNA of interest with the plastid genome because they have a DNA sequence that is homologous to the a part of the plastid genome. As plant parts include calli and as transformed plastid containing cells were produced from those calli (pg 51, lines 16-19), progeny were produced from the plant parts.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of lettuce plastid transformation taught by Koop et al, to use the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, sequences of interest providing herbicide resistance, and particle bombardment as the transformation method as described in Blowers et al. One of ordinary skill in the art would have been motivated to use the psbA terminator and particle bombardment as the transformation method because selection of terminator and transformation method from those commonly used in the art is an obvious design

choice. One of ordinary skill in the art would have been motivated to sequences of interest providing herbicide resistance because of agricultural practices that involve spraying herbicides on fields in which crop plants are growing.

One of ordinary skill in the art would have been motivated to use lettuce 70B/trnV/16S/trnI/trnA as flanking sequences because this region is commonly used in plastid transformation of other plant species. The exact breakpoint would be one of personal choice, and one of skill in the art would reasonably choose the breakpoint such that one flanking region comprises the trnI/trnA and the other 70B/trnV/16S. SEQ ID NOs:6-9 and/or 13-16 would thus be comprised within these sequences.

17. Claims 48 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201) as applied to claim s 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 above, and further in view of Daniell (WO 99/10513).

The claims are drawn to a method of transforming Asteraceae with a DNA of interest encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide.

The teachings of Koop et al are discussed above. Koop et al do not teach the DNA of interest encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide.

Daniell et al suggests expression of therapeutic or prophylactic (bio)pharmaceutical (poly)peptides, including edible vaccines, in plant plastids (pg 14, lines 13-22; pg 31, line 9, to pg 33, line 19).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transforming Asteraceae as taught by Koop et al to express a DNA encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide as described in

Daniell et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Daniell to express these proteins in plastids (pg 14, lines 13-22; pg 31, line 9, to pg 33, line 19).

18. Claim 53 is free of the prior art, given the failure of the prior art to teach or suggest a method of plastid transformation comprising culturing the transformed plastids of Asteraceae on media lacking a selection agent before selecting transformants with a light source corresponding to a visual marker. Claims 52 and 91-92 are free of the prior art given the failure of the prior art to teach or suggest a method of plastid transformation using a visual marker as a selection agent.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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June 19, 2008

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